Acetylcholine, Neurotransmitter

Abstract:

Acetycholine has been extensively studied for its role in cognitive function, memory formation attention processes, and sensory acuity. As a neurotransmitter, it exists throughout the body and is responsible for a number of physiological processes, diseases and disorders. This specific neurotransmitter has been studied across a number of different fields and been the subject of many published articles in journals that span from behavioral neuroscience, (neuro)pharmacology, psychology, physiology, neurochemistry, and neurobiology. The focus of this article is intended to examine the various physiological roles that acetylcholine is utilized in with specific regards to memory, recall, and learning. To begin, an overview of the research and developments in the scientific understanding of acetylcholine will be presented to provide an historical perspective over the decades of research that began in the early 20th century. It will then be narrowed to specifically legitimize or discredit claims made by a specific nootropic drug manufacturer that sells a product formulated to specifically enhance neural acetylcholine levels by various ingredients, of which the most important being are Vitamin B6, Alpha-GPC, Huperzine A, L-Tyrosine, and phosphatidylserine.

Introduction:

Choline is found in numerous sources and throughout all cells in the human body. Ingestion of choline can be derived from such foods as: eggs, poultry, meat, cruciferous vegetables, beans, and in the form of betaines (precursor to choline) in grains. [1] The mechanism by which acetylcholine is synthesized from choline involves the substrate acetyl-CoA and the enzyme choline acetyltransferase. [2] The cholinergic system is the most important biochemical and physiological pathways that is apart of our nervous pathway [3]. Another proposed mechanism is not yet verified, but suggested to arise from the presence of phosphatidylserine. The method by which phosphatidylserine would derive choline is as follows: 1) decarboxlyation of phosphatidylserine to phosphatidlyethanolamine 2) a 3 step reaction with the enzyme s-adenosylmethionine and substrate phosphatidylethanolamine to form ultimately form phosphatidylcholine, which can be degraded to choline. [2] Beyond the synthesis of acetylcholine, choline is necessary for phospholipids, as a consitutent in the structure of Very Low Density Lipoproteins (VLDL), and to aid in the livers function to excrete fat. [1]

Prior to the 1980s, it was understood that choline was present throughout the body, however, it was assumed that blood level concentrations varied between the brain and the body due to the Blood Brain Barrier. [2,4] This was found to be untrue, which then allowed scientists to make a stronger connection between acetylcholine deficiencies and various diseases and neurological disorders. [1,3,4] The ability to properly classify and locate the primary acetylcholine receptors types, muscarinic and nicotinic, was essential to the understanding of acetylcholine as a neurotransmitter. [ 3,4,5,6,7]

Acetylcholine receptors were first discovered and classified as a neurotransmitter in the 1930s by a team of researchers led by H.H. Dale at the National Institute for Medical Research.[5] In collaboration with another researcher at the National Institute, W. Feldberg, acetylcholine’s activity and presence in the body was beginning to be more widely understood. By the 1950’s the role of acetylcholine as a neurotransmitter was expanded to eventually include a presence in the central nervous system (CNS). Since that time, acetylcholine receptors have been found in the peripheral nervous system on nerves and muscles.[6,8] As a result of these receptors being present throughout the body, they are quickly becoming associated with diseases that result from autoimmune responses and genetic mutations. The side effects associated with said diseases is that of epilepsy, Alzheimer’s disease, Autoimmune myasthenia gravis, which presents itself as muscle weakness, Parkinson’s, Schizophrenia, and Tourette’s. [1,2,6, 8, 10, 11]

Acetylcholine Receptors, Distribution, Function and Disorders:

Nictonic acetylcholine receptors have been extensively studied due to the affinity for this receptor to bind with nicotine and acetylcholine. Nicotinic acetylcholine receptors are distributed throughout the brain and body in a yet unknown composition due to the sheer number of subtypes that exist. [4,6,12] Nicotinic acetylcholine receptors act as ligand ion channels. Some of the associated roles assumed by nictonic acetylcholine receptors are their role in physiological processes related to sleep, anxiety, working-memory, appetite, learning, and disease. [3,5,6,8,13] In greater depth, the neuronal nicotinic acetylcholine receptors in relation to the Central Nervous System, are necessary for the release of certain neurotransmitters like noradrenaline, enzyme processes and cell excitation [4] This receptor is not the only ion channel active in the brain and is genetically related to the gamma aminobutryic acid, glycine, serotonin, and 5-hydroxtryptamine channels. [3,6,12] Of the ligand ion channels found in our bodies, it is so well conserved over the span of evolution that it contains a greater than 80% genetic match across all the vertebrate species. [3]

The role of nicotinic acetylcholine receptors goes beyond the Central Nervous System and is present on muscle receptors and the nerves in the peripheral nervous system. [5,6] The research and advancement in identifying and locating the various types of receptors has revealed that there are 12 genes specifically coded for nicotinic receptors, alpha 2-10 and beta 2-4. [3] The specific role of each gene will not be discussed in depth as it goes beyond the scope of this paper. The neuronal receptors are also being revealed as synaptic responders capable of being influenced by acetylcholine not in its immediate vicinity [6]. The nicotinic receptors found outside of the brain have been linked to autoimmune myasthenia gravis which effects the skeletal muscle resulting in severe weakness and atrophy [6]. The relationship between neuronal receptors will be examined in greater detail.

The associated disease with nicotinic receptors in the neuronal cells are the degenerative disorders, such as, Alzheimer’s disease, Parkinson’s disease, epilepsy, autism schizophrenia and Tourettes [4,5,6,10] The relationship with epilepsy is not completely understood but it is proposed that as a result of acetylcholine receptors activating the release of gamma amino butyric acid and glycine this triggers epilepsy in the frontal lope of the brain [6]. In the case of Alzheimer’s disease, which is a neurodegenerative disorder with effects that many people are familiar with i.e. forgetfulness, anxiety, inability to learn, incapable of recognition, short-term memory loss. Previously it was hypothesized that cholinergic changes of the neural receptors led to this sort of disease. Stronger evidence suggests that it is a protein mediated disease, however, because treatment for Alzheimer’s disease is still undiscovered the focus on nicotinic receptors still remains as a form of treatment [4,5,6,8,9]. Parkinson’s disease is associated with the loss of nicotinic receptors and dopamine neurons. The effect of these losses results in impaired movement that is often shaky and lacking fine motor control. Interestingly enough, nicotine has a stimulating effect on dopamine counteracting one aspect of the disorder [6]. Similarly, the effects of nicotine are soothing with respect to the symptoms of schizophrenia and Tourette’s, which also has links to altered dopamine levels and nicotinic receptors found in the brain [6].

Muscarinic acetylcholine receptors are the second classification of receptor linked to acetylcholine and is required to activate pathways necessary for modulating synapses, neuron excitation, and feedback inhibition/regulation of acetylcholine [4,7]. They are guanine nucleotide binding proteins that are active in the Central Nervous system and peripheral nervous system [5,7]. Five genetic subtypes of muscarinic receptors have been classified and will be noted due to their associated importance with cognitive function [4,5,7]. As is the case with nicotinic receptors, and their location in the brain, it is especially difficult for researchers to localize and target due to the Blood Brain Barrier and it’s selective permeability [2,4,8,14].

It has been established that the M1 muscarinic neuronal acetylcholine receptor is associated with learning, memory, and motor activity. M2 has also been associated with memory[4]. Interestingly, in a clinical study conducted to treat patients with Parkinson’s disease, patients treated with agents meant to inhibit muscarinic receptors over a period of 2 years began to develop symptoms associated with Alzheimer’s disease [4]. The food uptake and appetite relationship that was found to be associated with acetylcholine receptors was linked to the M3 receptor in a study on mice. And the M4 receptor is responsible for dopamine receptor activation, which has been linked to the neuronal nicotinic receptor disorders schizophrenia and epilepsy [2,6,7]. Finally, the 5th and last subtype if the M5 muscarinic receptor is deemed to be necessary for dopamine release in the region of the brain called the striatum, also needed by the cerebral cholinergic induced vasodilatation of arteries [5,7]

Activators/Inhibitors and Cognitive Function:

Now that the types and distribution of acetylcholine receptors is broadly understood to be muscarinic and nicotinic, neural or peripheral, the specific ways in which enzymes, ligands, and drugs can target these should be highlighted. Acetylcholinesterase is an enzyme that hydrolyzes acetylcholine and produces acetate and choline [2]. Inhibiting this enzyme is a primary objective based on the assumption that acetylcholine is a neurotransmitter associated with cognitive function. [Et al] Cholinesterase inhibitors are currently being used to treat Alzheimer’s disease and have been approved by the United States Food and Drug Administration [15,16]. Due to the limitations of cholinesterase inhibitors, side effects, and success rate pharmacological research is still being focused on the specific subtypes of nicotinic and muscarinic receptors currently understood [10,5]

Scopolamine, atropine, oxotremarine, fluphenazine, pentylenetetrazole, orphenadrine, oxybutrin, and trihexyphenidyl are all agents designed and shown to disturb cognitive function as a result of altering acetylcholine receptors and concentrations [2,4,5,12] In contrast to these compounds, the acetylcholinesterase inhibitors tacrine, donepezil, galanthine, rivastigmine work to reverse the esterase enzyme and have been approved by the Food and Drug Administration for treatment of Alzheimer’s disease [2,15,16,17]. Another suggested method of boosting acetylcholine levels is through phosphatidylserine whose mechanism towards synthesizing acetylcholine was referenced earlier [1,2]. The importance of phosphatidylserine is that it has been postiviely associated with increased retention and absorption of passive and active tasks in rat studies [14]. It is also important to note that further inquisition into the efficacy of phosphatidylserine showed a decreased release of acetylcholine for brain samples in rats aged 24 months compared to those at 3 months [14]. This is especially important to consider due to the established connection between memory loss and aging [8].

Acetylcholine, through its long history and discovery, first as a neurotransmitter and then its associated disorders led to deeper research into its precise role in cognitive function. It is associated with learning, memory, recall, attention deficit disorder, stimuli detection, sensory processes, the circadian rhythm and motor function [8,9,10,18]. Acetylcholinesterases have been detected and quantified in a number of different regions of the brain: amyglada, hippocampus, cortex, striatum, medial septum, medulla oblongata, cerebellum, and hypothalamus [4,8,10,19]. Although acetylcholine has proven to be beneficial in cognitive function some studies have shown that modulating does within certain parameters increases how efficiently memory is stored [11].

Scopolamine has been shown in human subjects to negatively affect their sensory and attention processes as well as short-term memory. It has also been shown to induce negative effects that are more generally defined as aspects of learning and memory [4,8].The point to note about scopolamine and its effect on memory is that it only effects new memory acquisition, but does not alter the ability to recollect old memories. Nicotine and similar drugs work in the opposite manner by quickly targeting nicotinic acetylcholine receptors [13]. However, acetylcholinesterase inhibitors administered to test the ability of scopolamine and related enzymes reversed the effect of scopolamine and related target agents.[4,8,10].

Nootropics:

Nootropics are drugs broadly classified as effectors of cognitive functions. The side interactions of these drugs are not always well understood and as a result questions concerning the efficacy of such positively enhance cognitive effects is investigated [21]. The established acetylcholinesterase inhibitors tacrine, donepezil, galanthine, and rivastigmine are typically chosen as comparative measures to nootropic substances such as huperzine A, piracetem calcium blockers, or other extracts derived from plants [22].

The claims of nootropics has been countered on two primary accounts, the first is that anybody with diminished intellectual capabilities will be the best subjects to show any positive increase in mental performance. The second factor is that when a nootropic substance is tested on patients with Alzheimer’s disease is it targeting an age specific population group susceptible to a number of physiological alterations as a result of aging. Arousal is cited as a primary factor by which positive results will be obtained in test subjects. If a nootropic drug contains a compound or an unknown interaction that leads to arousal, cognitive function will be the enhanced [21].

One such study involving nearly 50 subjects effected by Alzheimer’s disease was began by removing all subjects from any acetylcholinasesterase inhibitors for 6-7 weeks prior to measuring cognitive ability [22]. The subject group was then split into two groups, one receiving nootropic ingredients, the other acetylcholinasesterase inhibitors. The results ultimately showed that the esterase inhibitors were more effective [22]. Another such study of more than 500 subjects revealed an inconsistency that is related to one of the reasons cited by Gainotti et al. in that the patients with mild Alzheimer’s showed a greater decrease in cognitive function while on nootropics. The study revealed that for moderately afflicted patients, the greatest decrease came from those who were on the esterase inhibitors and for the patients afflicted with the most severe case of Alzheimers, there was no difference. [22]

One nootropic extract, huperzine A, has been proven to be a more effective inhibitor of acetylcholineesterase activity than tacrine, donepezil, galanthine, and rivastigmine [15]. The levels of acetylcholine were also higher for a longer period of time as compared to the acetylcholinesterase inhibitors. The largest increase of acetylcholine levels compared to base levels was in the cortex, cerebellum and striatum, which in Alzheimer’s effected brains, the levels of acetylcholine is lowest in the striatum. [15]

### Onnit Labs – Alpha Brain:

### 

### With regards to the specific nootropic being market by Onnit Labs the following ingredient list will exhibit active substrates described to be effective. Vitamin B6, Alpha GPC (L-alphaglycerylphosphorylcholine), Huperzia Serrata (.5% Huperzine A), Vinpocetine , AC-11® ,Bacopa (50% Bacosides) ,Pterostilbene , L-Tyrosine, L-Theanine, Oat Straw (20:1), Phosphatidylserine. [23] The proposed benefits of a few ingredients will be highlighted as it pertains to the body of research.

Vitamin B6 is a cofactor in the production of the neurotransmitters gamma aminobutyric acid and dopamine [23]. The associated benefits of these two neurotransmitters being synthesized are that gamma aminobutyric acid and dopamine are associated with the nicotinic and muscarinic acetylcholine receptor diseases epilepsy, schizophrenia, and Parkinson’s disease [3,6,12]. The next ingredient listed is Alpha GPC which is a phospholipid containing a choline group that can pass through the selectively permeable Blood Brain Barrier [2,4,8,14,23]. Fortunately even if this proposed method of delivery does not work it has already been established that by simply raising blood choline levels after a meal, the brain choline levels will also increase [2]. However, the brain is typically at a higher concentration than the blood [2]. The next ingredient is probably the most important because of its specific testing done on Alzheimer’s effected persons and its comparative advantage to certain acetylcholinesterase inhibitors. Huperzine A was shown to be more potent than the common esterase inhibiting agents used (tacrine, donepezil, galanthine, rivastigmine) and also to have selectively increased acetylcholine levels in three regions of the brain [15]. Another ingredient to examine is L-tyrosine, which serves as a precursor to the neurotransmitter L-DOPA which becomes dopamine [23]. The final ingredient of any specific interest to the body of evidence supporting acetylcholine as a neurotransmitter that boosts cognitive function is phosphatidylserine. Phosphatidylserine is important as a phospholipid in the brain because increased amounts of this lipid have been shown to improve memory acquisition [1,2,14]. A reminder about phosphatidylserine’s importance is that 24 month old rats released a smaller amount of acetylcholine in comparison to younger rats and that aging and cognitive function are undeniably coordinated [8,14].

Based on the selected ingredients from Alpha Brain (Vitamin B6, Alpha GPC, Huperzine A, L-tyrosine, Phosphatidylserine) the literature from more than 80 years of research gives some support to the combination of substance used in this product. However, it seems that despite all of the research performed very few have begun to understand dosing amounts and what affects it has on consolidation of new information and recently formed memories. The majority of researches have only examined acetylcholine responses from rats and mice by methods of in vivo research. It is extremely difficult to know if the ingredients listed in the Onnit Labs nootropic formula will inhibit or activate accelerated neurotransmission or simply provide an energy boost akin to elderly Alzheimer’s subjects in nootropic studies using isolated extracts.

Conclusion:

After decades of research and the rapid growth of information regarding acetylcholine receptor locations, neural and muscular concentrations, functions, genetic make-up, and protein structure the information on this subject will only become more refined. The techniques will hopefully lead to a better understanding of neurodegenerative diseases such as Alzheimer’s, Parkinson’s, Tourette’s, schizophrenia, epilepsy and attention deficit disorders. Because, the cognitive relationship between acetylcholine and the regions of the brain responsible for memory formation, sensory input, attention processing, and recollection are understood well enough it would be beneficial to anyone that is interested in utilizing nootropic drugs, cholinesterase inhibitors, or cholernic agents to maintain higher levels of acetylcholine. Although older people would benefit most, it does not preclude anyone with a healthy functioning brain from giving it extra ingredients to help synthesize important amino acids, cell membranes, and neurotransmitters. It is a matter of trusting your sources and manufactures such as Onnit Labs to have produced a product with a blend of ingredients that is beneficial to cognitive function. Even if Onnit Labs formula does not contain enough active ingredients to have any noticeable effect, the ingredients extrapolated on in this paper and the ones unmentioned that are listed in Alpha Brain will likely benefit your health regardless of whether or not you feel a cognitive boost or new level of mental clarity. The science of neurobiology and physiology stands to gain a lot of scientific ground once something as well known and currently understood as acetylcholine and its many interactions are mapped out.

References:

1) Steven Zeisel “Choline”

* Advances in Nutrition. 2010 November; 1(1): 46–48.
* Published online 2010 November 16.<http://dx.crossref.org/10.3945%2Fan.110.1010>
* 2) Jan K. Blusztajn and Richard J. Wurtman “Choline and Cholinergic Neurons” *Science* , New Series, Vol. 221, No. 4611 (Aug. 12, 1983), pp. 614-620 Published by: American Association for the Advancement of Science
* <http://dx.doi.org/10.1126/science.6867732>
* 3) C. Gotti, F. Clementi “Neuronal nicotinic receptors: from structure to pathology”
* Progress in Neurobiology, Volume 74, Issue 6, December 2004, Pages 363–396
* <http://dx.doi.org/10.1016/j.pneurobio.2004.09.006>
* 4) Andrea Wevers “Localisation of pre- and postsynaptic cholinergic markers in the human brain” Behavioural Brain Research, Volume 221, Issue 2, 10 August 2011, Pages 341–355
* <http://dx.doi.org/10.1016/j.bbr.2010.02.025>
* 5) Daniel A Brown. “Acetylcholine” British Journal of Pharmacology. 2006 January; 147(S1): S120–S126. Published online 2006 January 9. <http://dx.crossref.org/10.1038%2Fsj.bjp.0706474>
* 6) Jon Lindstrom “Nicotinic acetylcholine receptors in health and disease”
* Molecular Biology. October 1997, Volume 15, Issue 2, pp 193-222
* <http://dx.doi.org/10.1007/BF02740634>
* 7) Chris J van Koppen, Björn Kaiser “Regulation of muscarinic acetylcholine receptor signaling” Pharmacology & Therapeutics, Volume 98, Issue 2, May 2003, Pages 197–220
* <http://dx.doi.org/10.1016/S0163-7258(03)00032-9>
* 8) Arjan Blokland “Acetylcholine: a neurotransmitter for learning and memory?”
* Brain Research Reviews. Volume 21, Issue 3, November 1995, Pages 285–300
* <http://dx.doi.org/10.1016/0165-0173(95)00016-X>
* 9) R.A. Hut, E.A. Van der Zee. “The cholinergic system, circadian rhythmicity, and time memory” Behavioural Brain Research, Volume 221, Issue 2, 10 August 2011, Pages 466–480
* <http://dx.doi.org/10.1016/j.bbr.2010.11.039>
* 10) Inge Klinkenberg, Anke Sambeth, Arjan Blokland “Acetylcholine and attention” Behavioural Brain Research, Volume 221, Issue 2, 10 August 2011, Pages 430–442
* <http://dx.doi.org/10.1016/j.bbr.2010.11.033>
* 11) Michael E Hasselmo. “The role of acetylcholine in learning and memory”
* Current Opinion in Neurobiology, Volume 16, Issue 6, December 2006, Pages 710–715
* <http://dx.doi.org/10.1016/j.conb.2006.09.002>
* 12) Martin Sarter, John P Bruno. “Cognitive functions of cortical acetylcholine: toward a unifying hypothesis”. Brain Research Reviews, Volume 23, Issues 1–2, February 1997, Pages 28–46
* <http://dx.doi.org/10.1016/S0165-0173(96)00009-4>
* 13) Michael E. Hasselmo, James M. Bower. “Acetylcholine and memory”
* Trends in Neurosciences, Volume 16, Issue 6, June 1993, Pages 218–222
* <http://dx.doi.org/10.1016/0166-2236(93)90159-J>
* 14) F. Pedata, L. Giovannelli, G. Spignoli, M.G. Giovannini, G. Pepeu
* “Phosphatidylserine increases acetylcholine release from cortical slices in aged rats”. Neurobiology of Aging, Volume 6, Issue 4, Winter 1985, Pages 337–339
* <http://dx.doi.org/10.1016/0197-4580(85)90013-2>
* 15) Rui Wang, Han Yan, Xi-can Tang. “Progress in studies of huperzine A, a natural cholinesterase inhibitor
* from Chinese herbal medicine”. Acta Pharmacologica Sinica 2006 Jan; 27 (1): 1–26 Blackwell Publishing
* <http://dx.doi.org/10.1111/j.1745-7254.2006.00255.x>
* 16) Antonio Contestabile “The history of the cholinergic hypothesis”
* Behavioural Brain Research Volume 221, Issue 2 10 August 2011, Pages 334–340
* <http://dx.doi.org/10.1016/j.bbr.2009.12.044>
* 17) Min-Young Noh, Seong-Ho Koh, Youngchul Kim, Hyun Young Kim, Goang Won Cho, Seung Hyun Kim. “Neuroprotective effects of donepezil through inhibition of GSK-3 activity in amyloid-β-induced neuronal cell death”
* Journal of Neurochemistry. Volume 108, Issue 5, pages 1116–1125, March 2009
* <http://dx.doi.org/10.1111/j.1471-4159.2008.05837.x>
* 18) Paul E. Gold “Acetylcholine: Cognitive and brain functions”. Neurobiology of Learning and Memory, Volume 80, Issue 3, November 2003, Pages 177

|  |
| --- |
| * <http://dx.doi.org/10.1016/j.nlm.2003.07.002> |

* 19) Maura L. Furey, Pietro Pietrini and James V. Haxby “Cholinergic Enhancement and Increased Selectivity of Perceptual Processing during Working Memory”. *Science* , New Series, Vol. 290, No. 5500 (Dec. 22, 2000), pp. 2315-2319 American Association for the Advancement of Science
* <http://dx.doi.org/10.1126/science.290.5500.2315>
* 20) Michael E. Hasselmo. “Neuromodulation: acetylcholine and memory consolidation”. Trends in Cognitive Sciences, Volume 3, Issue 9, 1 September 1999, Pages 351–359
* <http://dx.doi.org/10.1016/S1364-6613(99)01365-0>
* 21) Gainotti, G; Benedetti, N; Caltagirone, C; Nocentini, U. “Cognitive Improvement in Clinical Trials with Nootropic Drugs: When Can It Be Expected and How to Clarify Its Meaning”**.** Clinical Neuropharmacology, ISSN 0362-5664, 1986, Volume 9, Issue Sup 3, pp. S65 - 69
* <http://dx.doi.org/10.1097/00002826-198609003-00010>
* 22) M. Rainer, H. A. M. Mucke, C. Kruger-Rainer, E. Kraxberger, M. Haushofer, K. A. Jellinger. “Cognitive relapse after discontinuation of drug therapy in Alzheimer's disease: cholinesterase inhibitors versus nootropics.” Journal of Neural Transmission. November 2001, Volume 108, Issue 11, pp 1327-1333
* <http://dx.doi.org/10.1007/s007020100009>

23) Onnit Labs – Alpha Brain. Ingredients. 2012

* <https://www.onnit.com/alphabrain/#ingredients-use>